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Review Article

Optimization of pacing intervals in cardiac resynchronization therapy



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ABSTRACT

In patients with heart failure, left ventricular systolic dysfunction and prolonged QRS complex, cardiac resynchronization therapy (CRT) is a treatment method aimed at restoration of myocardial depolarization synchronicity. However, the extent of clinical and echocardiographic improvement depends on anatomical relations in individual patients, on structural changes in the heart, on intrinsic electrical activation, and on the position of pacing leads. Many parameters of CRT devices may be changed in order to tailor the function of CRT to the needs of a particular patient; the most important among them is AV and VV interval. The largest trials studying CRT used various methods for optimization of these intervals but unequivocal proof of the benefit brought by optimization is still lacking. Many methods were evaluated, most frequently based on echocardiography and intracardiac electrogram interval measurement. However, drawbacks in statistics make the studies of limited value for establishing a reference method or guidance for daily practice. Echocardiography has inherent variability of results and is highly operator dependent. Optimization based on intracardiac electrogram intervals has not proved yet to be of clear benefit above arbitrary AV interval. The most promising method is hemodynamic assessment by finger plethysmography. Measured data are highly reproducible and operator-independent. A randomized multicenter double-blind study using finger plethysmography is needed to prove the value of this method and of CRT optimization in general. The measurement of information content in any data suitable for CRT optimization, analysis of reproducibility and general usage of confidence intervals may show other methods appropriate for it, too. The cooperation with a statistician is oftentimes a necessity.

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1. Introduction

Cardiac resynchronization therapy (CRT) has become one of the fundamental therapeutic methods in patients with heart failure, left ventricular dysfunction and QRS prolongation. The aim of CRT is to restore ventricular electrical activation timing and thus to improve left ventricular mechanical coordination. Unfortunately, full restoration with CRT is not possible – an intact His-Purkinje system cannot be completely substituted by any means. CRT devices have several pacing intervals, AV and VV intervals in particular, which may be optimized according to the individual patients' needs. Individual patients may differ not only in the intrinsic activation sequence and velocity but also in lead location or in the distribution of scars after myocardial infarction, which may require different AV and VV interval settings to maximize the effect of resynchronization. The aforementioned facts were probably well known to the authors of the largest studies proving clinical effect of CRT: COMPANION [1,2] and CARE-HF [3,4]. The pacing interval optimization was performed in both of them. However, the optimization is difficult in daily clinical practice; it is time consuming and lacks any approved standardized method. One can get a time estimate for optimization from a study by Brignole who used tissue Doppler technique for VV interval optimization and pointed out its relative simplicity. Time required for the optimization of this interval in one patient was less than 60 min [5]. But the wealth of methods available for the measurement of the impact of pacing on hemodynamics is really great.

2. Invasive methods of CRT optimization

Only the maximum of the first derivative of left ventricular pressure (dp/dt_{max}) has reached broader acceptance. This parameter serves as an index of contractility, unfortunately not independent. The Frank-Starling law teaches us that myocardial contractility is preload dependent, a Bowdich or staircase phenomenon describes that contractility increases with the heart rate, and finally, afterload increases contractility as well (Anrep effect). dp/dt_{max} is rarely used in clinical practice [6]; its role is more in validation of other methods. It is oftentimes measured with inductance catheters together with stroke volume and other hemodynamic variables [7].

3. Echocardiographic methods of CRT optimization

3.1. Methods using the mitral inflow pattern

The aim is to set the AV delay so that the untruncated A wave ends in the moment of mitral valve closure. The most straightforward way is to search for it by iterative changes in the AV delay under echocardiographic guidance (iterative method). To reach the same goal just from the measurements during two AV delays, from a “too long” AV delay and a “too short” AV delay, Ritter's method can be used. It was developed in patients with dual chamber pacemakers and published as an abstract in 1994 [8]. Optimal AV delay (AV_{opt}) is calculated according to the equation

$$AV_{opt} = AV_{long} - (QA_{short} + QA_{long})$$

where QA_{short} stands for the interval between the QRS onset and the end of A wave during pacing with “short” AV delay (this interval represents approximately the delay between electrical and mechanical systole). Then, during pacing with “long” AV delay (AV_{long}) QA_{long} represents the interval between mitral valve closure and the QRS onset. The sum of $QA_{short} + QA_{long}$ is subtracted from AV_{long} and the result is AV_{opt} (Fig. 1).

Another way to calculate optimal AV delay in patients with systolic mitral regurgitation without time consuming iteration was published by Meluzin [9]. First step is to measure the longest AV delay with full ventricular capture. Then, this value is decreased by 5–10 ms to so called “testing long AV delay”, and the time interval from the end of the A wave to the onset of the systolic component of mitral regurgitation (time t_1) is measured at this setting. The optimal AV delay is calculated as “testing long AV delay” – time t_1 (Fig. 2).

3.2. Methods quantifying the aortic outflow or mitral inflow

Blood flow through the left ventricular outflow tract (LVOT) during one cardiac cycle can be measured using velocity–time integral (VTI). VTI in LVOT (VTI_{ao}) is frequently used as a surrogate for stroke volume [10]. The aim of the optimization is to reach the largest area under the curve which indicates the highest stroke volume. The method is used not only for AV but for also VV optimization (Fig. 3).

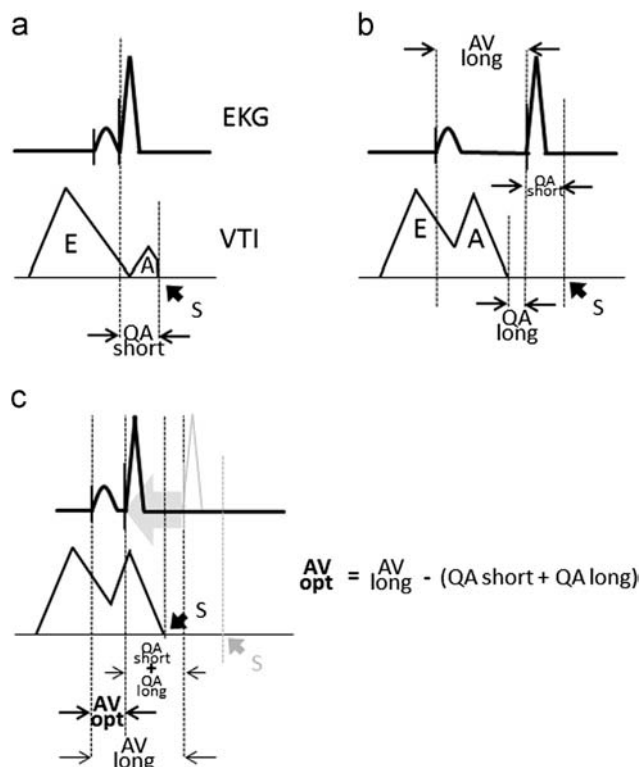


Fig. 1 – Ritter's method for AV optimization: AV_{long} – long AV delay, AV_{opt} – optimal AV delay, QA_{short} – interval between QRS onset and the trimmed end of A wave, QA_{long} – interval between the end of A wave and the onset of QRS, E – E wave, A – A wave, S – beginning of mechanical systole (the moment of mitral valve closure). (Adapted from Melzer [63]).

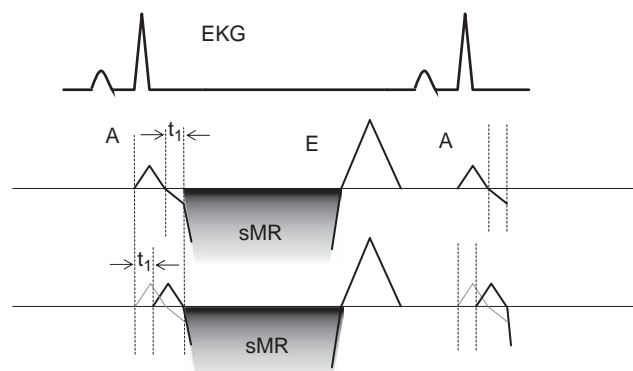


Fig. 2 – Meluzin's method for AV delay optimization. A – A wave, E – E wave, sMR – systolic mitral regurgitation, t_1 – time interval between the end of A wave and the onset of mitral regurgitation (adapted from Meluzin [9]).

VTI in the mitral inflow region is used for optimization less frequently [11].

3.3. Methods for quantification of dyssynchrony

The main goal of resynchronization is to restore mechanical synchrony of contraction between left ventricular septum and the free wall. The VV interval can be optimized according

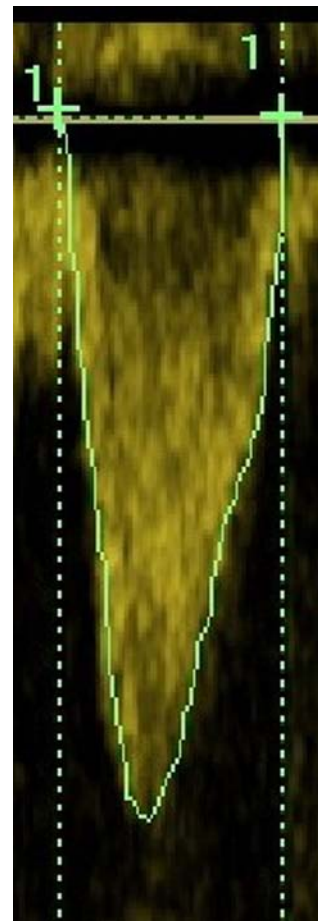


Fig. 3 – Measurement of time-velocity integral of the flow in the left ventricular outflow tract (VTIao) obtained by Doppler echocardiography. Time-velocity integral – the area under the curve of a Doppler signal in the left ventricular outflow tract (VTIao). (Figure by courtesy of Dr. Lhotsky).

to the left ventricular lead location and the speed of the mechanical contraction wave. The dyssynchrony measurement is mostly based on tissue Doppler techniques (TDI). Jose Brugada and his group published a study using the comparison between septum and lateral wall in apical four-chamber view and between anterior and inferior wall in apical dual-chamber view [12]. Another group optimized VV interval by measuring dyssynchrony in 6 basal segments [5]. Speckle tracking is a newer method with similar goals using different principle to visualize mechanical activity of the ventricular myocardium. The use for CRT optimization was published only in individual patients [13]. Three-dimensional (3D) echocardiography has rarely been used for optimization so far [14].

3.4. Tei-index

Tei-index (myocardial performance index – MPI) is a parameter of heart function, which is relatively easy to measure. It is calculated according to the equation [(isovolumic contraction time+isovolumic relaxation time)/ejection time]. It was used rarely for CRT optimization [15,16].

4. Other non-invasive methods

4.1. Non-invasive cardiac output measurement

Much effort has been made to measure cardiac output using methods less invasive and less demanding than Fick principle, dye-dilution or thermodilution. Semi-invasive system LiDCO calculates beat to beat changes of stroke volume from the arterial pulse wave obtained using an arterial cannula. For absolute values, the system must be calibrated by applying lithium chloride intravenously. The system was used for CRT optimization only rarely [17].

Another option for fully noninvasive cardiac output measurement is bioimpedance. For CRT optimization, Task Force Monitor (CNSystems, Graz, Austria) [18–20], BioZ (CardioDynamics, San Diego, USA) [21] or NICOM (Cheetah Medical, Vancouver, USA) [22] were used.

Different principle is applied in the Innocor system (Innovision, Odense, Denmark). The device measures the changes in concentration of two inert gases during short-term rebreathing. The rebreathing bag is prefilled with an O₂ enriched mixture typically containing 0.5% nitrous oxide (N₂O) which is blood soluble and 0.1% sulfur hexafluoride (SF₆) which is blood insoluble. The concentration change of SF₆ during rebreathing is measured to determine the lung volume and to account for other factors that affect the distribution of the blood soluble gas. The diminishing concentration of N₂O during rebreathing reflects the blood flow through the lungs. When there are no AV shunts the blood flow through the lungs equals cardiac output. Several studies used this method for CRT optimization [23–25].

4.2. Noninvasive blood pressure measurement

Beat to beat measurement of blood pressure changes is usually based on finger plethysmography. The fundamental principles were developed by Prof. Peňáz (Brno, Czech Republic). CRT optimization was performed using Finometer (FMS Amsterdam, The Netherlands) and Nexfin (BMEYE, Amsterdam, The Netherlands) [26,27].

4.3. Acoustic cardiography

Acoustic cardiography is based on the measurement of the time interval between the QRS onset and mitral component of the first sound. CRT optimization was mostly done with AUDICOR TS (Inovise Medical, Beaverton, USA) [28–31]. The same principle was used in the study by Miki; the microphone was connected to the audio input of the echocardiographic machine [32]. Similar principle was applied in sonR – a sensor commercially available for optimization in the CRT devices from Sorin Group [33].

4.4. Methods based on the ECG or intracardiac ECG analysis

The most simple method for VV interval optimization is based on the QRS complex duration measurement [34–36]; experience with morphological criteria is limited [37]. Barold

and his group published a study, where the VV interval was set according to the latency of pacing from both right ventricular and left ventricular leads [38].

Methods based on intracardiac ECG (IEGM) interval measurement have an advantage in easy incorporation into the CRT devices. QuickOpt algorithm (St. Jude Medical) uses atrial depolarization duration measured in the RV lead for the AV delay calculation. Sensed AV delay equals atrial depolarization duration plus specific increment that depends on the duration of atrial depolarization. If it is ≥ 100 ms the algorithm adds 30 ms; if it is < 100 ms the algorithm adds 60 ms. In case of atrial pacing instead of sensing, another 50 ms are added to the AV delay. VV interval is calculated according to the equation

$$(VV = 0.5(\Delta + \epsilon))$$

where $\Delta = R_{LV} - R_{RV}$ (R_{LV} and R_{RV} stands for local activation detected by LV or RV lead), and $\epsilon = \text{plVCD}_{LR} - \text{plVCD}_{RL}$, (plVCD_{LR} is the interval between the pace in LV to the sense in the RV lead whereas plVCD_{RL} is the interval between RV pace and LV sense) [39–43].

SmartDelay (Boston Scientific) calculates the AV delay during atrial sensing (SAVD) or atrial pacing (PAVD) as follows:

$$\text{SAVD} = K1 \times \text{QRS} + K2 \times \text{SAVI} + K3$$

$$\text{PAVD} = K1 \times \text{QRS} + K2 \times \text{PAVI} + K3$$

where SAVI and PAVI are intervals between sensing (SAVI) or pacing (PAVI) in the atrium and sensing in the RV; K1, K2 and K3 are coefficients taking the lead location into account – details and experimental testing of the algorithm were described in detail by Gold [44].

The aCRT algorithm (Medtronic) periodically updates intrinsic AV interval, determined as the time from the atrial sensing or pacing to the RV sensing, P-wave conduction interval, determined as the time from atrial sensing or pacing to the end of the P wave in the far-field electrogram, and QRS conduction interval determined as the time from the RV sensing to the end of the QRS complex in the far-field electrogram. If the intrinsic AV interval during atrial sensing is normal (≤ 200 ms) and the heart rate does not exceed 100/min, the algorithm uses only LV pacing with preempt intrinsic conduction by at least ≥ 40 ms. Otherwise, the algorithm switches to biventricular pacing with the AV delay calculated from the intrinsic A-RV to pace after the completion of the P wave but to preempt intrinsic RV sensing by at least 50 ms. V-V interval is calculated from the QRS duration. Basic principles were published by Krum [45].

5. Clinical significance of pacing intervals optimization

The aforementioned list of methods, which is far from being complete, documents the effort which was invested into pacing interval optimization. But is there any evidence about the benefit brought by optimization? Very few multicentric randomized double blind studies were published. Sawhney in 2004 in an unicentric randomized controlled single blinded study showed that AV optimization with VTlao improved LVEF, NYHA class and quality of life after 3 months of follow-up when compared with empiric AV delay at 120 ms [46].

In 2010, Ellenbogen published the results of SMART-AV trial – a multicentric double-blind study in 980 patients randomized to either empiric AV delay of 120 ms, to AV delay optimized according to the mitral inflow pattern (iterative method) or to the SmartDelay algorithm. Primary endpoint was the change in left ventricular endsystolic volume (LVESV), secondary endpoints were the change in NYHA class, quality of life, 6-min walking test and left ventricular enddiastolic volume of the left ventricle. Optimization did not improve any of the endpoints in the optimized arm above the results of the empiric AV delay arm [47,48].

FREEDOM trial was a multicentric randomized prospective double blind study with the hypothesis that frequent AV and VV optimization using QuickOpt is better or is not worse than empiric AV delay or AV delay optimized by some other method not based on IEGM. The results were presented by Abraham at HRS Meeting 2010 and are available after registration on the web pages of St. Jude Medical. The trial randomized 1525 patients either to QuickOpt algorithm or to the control group where either empiric AV delay was programmed (470 persons) or optimization was performed only at the beginning of the study (274 persons). After 12 months of follow-up, no significant difference between groups could be found [49].

Multicenter randomized studies limited only on VV optimization are rare. RHYTHM II ICD trial was multicentric single-blinded study in 121 patients with AV delay optimization using the pattern of mitral inflow who were randomized in 3:1 ratio to the VV optimization using VTlao or simultaneous ventricular pacing. After 6 months of follow-up, no difference in reverse remodeling between both groups was observed [50,51].

Rao in 2007 published results of DECREASE-HF which was a multicentric randomized double-blind study with 306 patients who were implanted with Contak Renewal 2/4/4HE and randomized either to simultaneous biventricular pacing or to sequential biventricular pacing or LV pacing only. The optimization was performed using the algorithm ExpertEase implemented in the device. Patients with sequential ventricular pacing had LV preexcitation in the range 20–80 ms, and individual intervals were selected according to the algorithm based on IEMG intervals which was developed on hemodynamic data from PATH-CHF. After 3 and 6 months of follow-up, stroke volume and ejection fraction increased in all groups. The decrease in LVESV was most pronounced in the group with simultaneous biventricular pacing [52].

A multicentric, randomized, double-blind noninferiority Adaptive CRT Study evaluated the aCRT algorithm. It included 522 patients who were randomized in 2:1 ratio to the aCRT algorithm or to the optimization using echocardiographic parameters – the iterative method for AV delay and VTlao for VV interval. There were three endpoints: clinical composite score (CCS) used in multiple CRT trials reflecting overall course of the disease (death, hospitalization for heart failure or worsening of heart failure); concordance correlation coefficient between VTlao and aCRT algorithm; safety of a CRT algorithm. During 6 months of follow-up, all three primary objectives were met [53].

Another small unicentric double-blind crossover study included 24 patients who were optimized using Innocor.

Optimal pacing intervals significantly increased exercise tolerance [23].

The aforementioned data show that methodically strict studies do not unequivocally prove the benefit from CRT optimization. However, the number of studies is limited and majority of them dealt with IEGM based algorithms incorporated in CRT devices.

6. The comparison of the most frequently used optimization methods

The algorithms implemented into the CRT devices are quite easy to access and use. SmartDelay in SMART-AV was shown to be as good as empiric AV delay of 120 ms. QuickOpt algorithm was very promising in the beginning. Baker found very good correlation between this algorithm and VTlao [54]. In another study, very good concordance between this algorithm and 3D echo was found [39]. An agreement with the results of this algorithm and other echocardiographic methods was achieved in several studies [40,55]. However, FREEDOM trial has cast some shadow on this algorithm [49].

Second place in the frequency of use belongs to echocardiographic methods. The most simple may appear to be Ritter's method. Limitations can be in the difficulty to find the exact end of the A wave; frequently at least limited iteration is necessary. A fundamental problem is that the mitral wave closure at the end of A wave does not correlate with the highest dP/dt_{\max} in the left ventricle, it is usually close to the top of A wave [56].

VTlao is not free of problems either. Whereas Thomas in his study says that “Left ventricular outflow tract VTI provides us with a single, direct measure of global LV function which is robust, and easily applicable in routine clinical practice, and which is effective at improving response to CRT” [57], Zuber finds the reproducibility of VTI very limited [31]. High variability in results was found by Whinnett as well [58]. In one study, mathematical modeling based on published data from another study showed that utility of VTlao for CRT optimization might be limited [59].

7. What to do in daily practice?

Two problems must be taken into account when we think about the optimization methods. First, the human body represents a system inclined to equilibrium. Francis' group which published a series of papers about finger plethysmography optimization demonstrated that blood pressure change accompanying the pacing parameters change is only temporary [60,61].

Second, we should be aware of the limitations of a particular method. This concept developed by Francis operates with the term of information content. Every measured parameter has some random noise and some information. The proportion of the information in the signal is the information content (range 0–1):

$$\text{information content} = \frac{\text{signal variance}}{(\text{signal variance}) + (\text{noise variance})}$$

Variance, one of the basic statistical terms, is defined as follows:

$$\text{variance} = \frac{\sum_0^n (x_n - \bar{x})^2}{n}$$

Information content can be measured in every lab using repeated measurements. To give an example, let us imagine that we optimize AV delay. We perform 4 measurements with AV delay at 100 ms, 4 measurements with AV at 120 ms and 4 measurements with the AV delay at AV 140 ms. Information content is calculated according to the equation

$$\text{information content} = \frac{R}{R-1} \frac{V_m}{V_{\text{raw}}} - \frac{1}{R-1}$$

where R is the number of repetitions ($R=4$ in our hypothetical measurement), V_{raw} is the variance for all data, i.e. for 12 values from their mean and V_m is the variance of the means for every AV delay (3 means, i.e. for 100, for 120 and for 140 ms) from the mean of these means (which is the same as the mean of all 12 values). In this particular case, the calculation will be based not on the absolute blood pressure values measured during pacing with AV delays at 100, 120 and 140 ms on but the difference of systolic blood pressure between arbitrarily selected reference AV delay, let's say 160 ms, and the value under examination (100, 120 and 140 ms) as explained below.

It is difficult to define the minimum value of information content for meaningful measurement. Simplifying the situation as much as possible, one could conclude that for AV delay optimization, the information content below 0.4 makes the measurement useless even with a clinically feasible number of repetitions [59]. Provided we have some data obtained from repeated measurements, validation of the significance can be done using confidence intervals (CI). The CI of 95% is calculated as $\text{mean} \pm 1.96 \times \text{standard deviation (SD)}$. SD is just a square root of the above mentioned variation.

A meaningful procedure can be accomplished only using methods with proven reliability. Assessment of the methods based on visual analysis of a signal, like Doppler recordings or QRS complex duration measurements, must therefore be done blindly to quantify the information content correctly. Operator-independent methods (e.g. automated device measurements) should reach stable information content when meticulously applied. Finger plethysmography is the most extensively investigated method so far. After series of studies, Francis' group came to the conclusion that the best parameter for CRT optimization is systolic blood pressure, followed by pulse pressure and mean arterial pressure [62]. Because of spontaneous fluctuations in physiologic parameters, only the differences of values caused by a change in parameters like the change in blood pressure between randomly selected reference AV delay and evaluated AV delay can be used. Last six cycles before and immediately after parameter change should be used for calculation, even better but rather demanding is respiration cycle synchronization [59]. Adherence to these rules provides reliable and reproducible data. Obviously, all signal-processing issues of proper optimization based on finger plethysmography can only be implemented with the help of automatic or semiautomatic computer algorithms. The validation of preliminary results in independent studies is necessary prior to development of commercially available

optimization systems. Unlike finger plethysmography, most reports on other optimization methods published so far did not meet the requirements of statistical verification which would prove their reliability. A multidisciplinary approach with a statistician on board is essential for introducing new optimization strategies into clinical practice.

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